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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/595,495	04/24/2006	Nicolas Mermod	3024-119	1575

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EXAMINER	
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ART UNIT	PAPER NUMBER
1636	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/595,495	MERMOD ET AL.	
	Examiner	Art Unit	
	CELINE X. QIAN	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-17,23,24,26,34,42-45,48,49,51,55 and 62-115* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *65-91,101-108 and 111-115* is/are rejected.

7)☒ Claim(s) *69,72,73,80,82,90,103,104,106 and 107* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 April 2006* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *0107, 0607,0707,0408,0409*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 15-17,23,24,26,34,42-45,48,49,51,55,62-64,92-100,109 and 110.

DETAILED ACTION

Claims 15-17, 23, 24, 26, 34, 42-45, 48, 49, 51, 55, 62-115 are pending in the application.

Election/Restrictions

Applicant's election with traverse of Group I in the reply filed on 10/20/08 is acknowledged. The traversal is on the ground(s) that in all claims of Group I and III claims, Applicants clarified the nature of at least one MAR element and/or its relationship to cLysMAR. Applicants further assert that the sequences share the activity of increasing protein production and, feature a high A and T content, a structural element recognized in the art for MAR sequences. Applicants argue that according to Section (f)(i)(B)(1), there is no indication when common chemical structure occupies a large protein, that the Administrative Instructions require a common core sequence as set forth by the office action.

The above arguments have been fully considered, but they are not found persuasive. The invention of Group III and the newly added claims 65-92, 101-107 and 111-115, allegedly belong to the invention of Group I, do not share the same corresponding technical feature because the special technical feature of Group III is directed to either a sequence comprising a bendable DNA that comprises 10% TA and or 12% TA, one or more sequences of SEQ ID NO: 1-27 and fragments thereof, or a synthetic MAR sequence comprising natural human MAR elements or fragments assembled between linker sequence. This special technical feature does not make a contribution over prior art because Klehr et al. (see IDS) disclose synthetic MAR comprising human β-interferon Domain MAR comprising linker such as EcorRI and

BamHI (see page 1265, 2nd col., 1st paragraph, and Figure 1). Therefore, this special technical feature does not linked claims of Group III and I to form a single general inventive concept under PCT 13.1. In response to argument directed to the requirement for electing one nucleic acid sequence, Applicants are first reminded that this election is not an election of species, rather, it is a restriction requirement (see page 3, 3rd paragraph, line 11). Further, while the Administrative Instruction does not assert that the common chemical structure require a common core sequence, in the context of MAR DNA sequence, the chemical structure is defined by the sequence and secondary structure. The guideline requires that all alternatives must share a common property and a common structure. Therefore, the claimed sequences with different SEQ ID NO do not share a common structure because they do not share a significant structural feature that is a contribution over prior art. Therefore, the restriction requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 15-17, 23, 24, 26, 34, 42-45, 48, 49, 51, 55, 62-64, 92-100, 109 and 110 are withdrawn from consideration for being directed to non-elected subject matter. Claims 65-91, 101-108 and 111-115 are currently under examination.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (for example, see page 3, line 2). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

The use of the trademark such as SMARTSCAN has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Objections

Claims 69, 72, 73, 80, 82, 90, 103, 104, 106, 107 are objected to for containing non-elected subject matter. Applicants elected SEQ ID NO: 25 for examination. Amending the claims such that they are only directed to elected inventions is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 65-91, 101-104, 112-115 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The written description requirement is set forth by 35 U.S.C. 112, first paragraph which states that the: "*specification* shall contain a written description of the invention. . .[emphasis added]." The written description requirement has been well established and

characterized in the case law. A specification must convey to one of skill in the art that "as of the filing date sought, [the inventor] was in possession of the invention." See *Vas Cath v. Mahurkar* 935 F.2d 1555, 1560 19 USPQ2d 1111, 1117 (Fed. Cir. 1991). Applicant may show that he is in "possession" of the invention claimed by describing the invention with all of its claimed limitations "by such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed invention." See *Lockwood v. American Airlines Inc.* 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997).

In analyzing whether the written description requirement is met, it is first determined whether a representative number of species have been described by their complete structure. Next, it is determined whether a representative number of species have been sufficiently described by other relevant identifying characteristics. Claim 65 recites "a purified and isolated DNA sequence that comprises at least one bent DNA element comprising at least 10% of the TA and/or 12% AT on a stretch of 100 base pairs, and at least one binding site for a DNA binding protein, which has protein production increasing activity greater than that of cLysMAR." The claimed invention encompasses a large genus of nucleic acid sequences of varying length (longer or equal to 100 base pair) which have at least 10% of the TA and/or 12% AT on a stretch of 100 base pairs, regardless whether they possess protein production increasing activity greater than that of cLysMAR in any setting (*in vitro, in vivo*, or in transgenic organism). The specification discloses identification of MAR sequences which may increase protein expression in CHO cells through bioinformatics computational algorithms. The specification discloses 4 sequences (1-68, 1-6, 1-42 and X-S29) picked out from such potential MARs which

displays protein production increasing activity greater than that of the 5' chicken lysozyme MAR when linked to the expression construct in CHO cells. The specification discloses all these sequences have a high AT/TA value (mean about 35%, see Table 6) and comprises potential transcription factor binding sites. However, the specification does not disclose whether any sequence with 10% TA and/or 12% AT on a stretch of 100 base pairs and a DNA binding site would have protein producing increasing activity in any setting (*in vitro, in vivo* or in transgenic organism).

The information within the prior art at the time of filing does not make up for the deficiency in the specification for describing the structural element that is linked to the claimed function. The specification indeed states in the background section "no clear cut MAR consensus sequence has been found...(page 2, line 37)" and "the identification of MAR by biochemical studies is a long and unpredictable process, various results can be obtained depending on the assay (see page 2, lines 46-47)." With regard to predicting MAR sequence by *in silico* method, the specification teaches all available tools are limited by factors such as poor specificity, the lack of confirmation of large amount of hypothetical MARs identified by such tool, and thus, many of such tools becomes useless to identify potent genetic elements with regard to efficient increasing recombinant protein production (see page 3, 1st-3rd paragraph). Girod et al., published in 2007 (see IDS), 4 years after the date of filing of the present application, state "only a few MARs have been conclusively identified from an estimated number of 50,000 or more per genome." Girod et al. further teach that "although the nuclear matrix binding function of MARs is conserved from plants to mammals, their DNA sequence is highly polymorphic, and their activities could not be ascribed to any simple DNA motif. Thus, MAR function has often

been related to structural properties rather than to its primary sequence, such as the high DNA strand unwinding and unpairing susceptibility of A+T rich sequences and a high potential for denaturation of the double helix. Whether these features contribute to the transcriptional activity of MARs is yet unknown." Girod et al. then teaches a method of identifying MAR sequences based on the prediction of active MAR sequences have a high potential to accommodate curvature, a deep DNA major groove and a wide minor groove, a weak correlation with DNA melting temperature and the presence of certain transcription factors such as SATB1, NMP4 and homeobox proteins (see page 748, 2nd col., and page 749). Girod et al. disclose that 1,566 sequences from the human genome were identified using above parameter at stringent condition (see page 749, bridging paragraph). Girod et al. disclose that none of the 1,566 sequence can be completely aligned on the mouse genome, and suggesting different primary sequence may contribute to species specificities. Girod et al. further selected several putative MAR sequences based on the basis of their high computed score, location near known ubiquitously expressed genes (to avoid tissue specific activity), and have core elements of various length and/or enriched in various combination of potential transcription factor binding sites (see page 749, last paragraph of col.2). Girod et al. disclose that 6 out 7 such sequences increased expression of a reporter in stably transfected polyclonal CHO cells substantially. Girod et al. disclose that one of the non-activator, 1-15, does not exhibit obvious difference between active and inactive sequences, wherein it also has highly enriched AT and TA dinucleotides (70%), and no qualitative or quantitative difference between core sequences of functional and inactive sequences. Girod et al. assert that the mere presence of an (A+T) rich core elements does not suffice to activate gene

expression, and the lack of activity may result from the lack of tissue specific activities in CHO and/or from the requirement of additional DNA features (page 750, 2nd col., 2nd paragraph). Girod et al. suggest that gene activation by MARs may rely on the positioning of a nucleosome in the vicinity of transcription factor binding sites, whereas DNA curvature motif alone is not sufficient for transcriptional activity (see page 752, 1st col., 1st paragraph). Girod et al. acknowledges that MARs display a bewildering array of activities that have been difficult to ascribe to any specific DNA motif (see page 751, 2nd col., 1st sentence of last paragraph).

In view of the teaching in the prior art, it appears that there is no consensus agreement that any of the specific DNA motif may be ascribe to various activities of MARs, especially the protein expression enhancing activity. As such, whether a DNA sequence comprising one bent element comprising at least 10% of the dinucleotide TA an/or at least 12% of the dinucleotide AT on a stretch of 100 contiguous base pairs; and at least one binding site for a DNA binding protein can increase protein production is unpredictable. The specification discloses only 4 (4 out of more than one thousand that selected by the computer program) nucleic acids that have the recited structural and can increase protein production in CHO cells greater than that of cLysMAR, it thus fails to describe a representative of species of nucleic acids having the structural properties comprising at least 10% of the dinucleotide TA an/or at least 12% of the dinucleotide AT on a stretch of 100 contiguous base pairs; and at least one binding site for a DNA binding protein that can have the functional property of increasing protein production in any system than that of cLysMAR. Moreover, the specification fails to describe other identifying characteristic of the claimed genus of nucleic acids that has the recited

structure and function. In other words, the specification fails to describe a nexus between the claimed structure and the function of increasing protein production in any system than that of cLysMAR. Nucleic acids that of various lengths (larger or equal than 100 base pair) comprise 10% of the dinucleotide TA an/or at least 12% of the dinucleotide AT on a stretch of 100 contiguous base pairs may have the property of being a curved DNA and/or bind matrix protein (DNA binding protein is not limited to transcription factors, but applies to matrix binding protein as well), whether they have the function of increase protein expression *in vitro* (in cell free system) or *in vivo* or more than that of cLysMAR is unpredictable because the specification fails to establish such a nexus. Similarly, although the art recognizes that the MARs having transcription activity generally has a wider minor groove and deeper major groove and a low melting temperature, the exact value for such parameters possessed by a nucleic acid molecule that has protein increasing activity greater than that of cLysMAR is not precisely determined even years after the application is filed. The application also fails to describe such parameter for the claimed genus of nucleic acids that alleged have protein production increasing activity greater than that of cLysMAR. Since the specifications fails to establish a structural and functional relationship, and the prior art does not make up such deficiency, the skilled artisan would not be able to envision the common structure of the claimed nucleic acid required for its function. Therefore, the claimed DNA is not sufficiently described by the instant specification. With regard to variants or fragments of SEQ ID NO: 25, it is not sufficiently described because the specification does not describe which fragment, and or what type of variant of this DNA molecule have the protein producing increasing activity. Lastly, since the claimed DNA is not sufficiently described, the vector and host cell

comprise said DNA also lack description for same reason as set above. Thus, the specification fails to describe the invention in such a way to convey a skilled artisan that the inventors had possession of the invention at the time the application was filed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 65-91, 101-104 and 107 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 65 and 101, the word "cLysMAR" renders the claim indefinite because it is unclear what the word stands for. Abbreviation is permitted in the claim, however, it must be spell out for the first appearance for determining the metes and bounds of the claim. Claims 66-91, 101-104 are rejected for same reason because they depend on claims 65 and 101.

Regarding claim 107, the term "BglII-BamHI linker" renders the claim indefinite because it is unclear whether the human MAR elements is located between BglII and BamHI or between BglII and BamHI linker on each side.

Claim s 81 and 82 recites the limitation "said second purified and isolated DNA sequence" in line 1. There is insufficient antecedent basis for this limitation in the claim because claim 74 only recites one purified and isolated DNA sequence.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 105, 106 and 108 are rejected under 35 U.S.C. 102(b) as being anticipated by Klehr et al. (see IDS)

Klehr disclose synthetic MAR comprising human β-interferon Domain MAR comprising linker such as EcorRI and BamHI (see page 1265, 2nd col., 1st paragraph, and Figure 1). Since the specification does not describe what constitutes a variant of SEQ ID NO: 25, the disclosed MAR from Klehr et al. is considered to meet this limitation. Claim 108 is a product by process claim, the process of how the product is made (claim 15) does not impart a structural difference from the prior art disclosed MAR. Therefore, Klehr disclose the instantly claimed invention.

Claims 112-115 are rejected under 35 U.S.C. 102(b) as being anticipated by Michalowski et al (US 6,245,974).

Michalowski et al. disclose isolated MAR DNA sequences comprising at least 33% of the dinucleotide and/or at least 33% of the AT on a stretch of 100 contiguous base pairs; and at least one binding site of a DNA binding protein (see for example, Figure 4, SEQ ID NO: 5, 20, etc). Michalowski et al. also disclose vector constructs comprising said MAR and a gene of interest, and vector comprises multiple MAR (see col.1, lines 45-56). Michalowski disclose said MARS increases reporter expression in

stably transformed cell line (see Example 5). Therefore, Michalowski et al. disclose the instantly claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 107 is rejected under 35 U.S.C. 103(a) as being unpatentable over Klehr et al.

The teaching of Klehr et al. was discussed above. However, Klehr et al. do not teach a MAR with BglII-BamHI linker.

It would have been obvious to an ordinary skill in the art to add a BglII-BamHI linker to a synthetic MAR sequence based on the choice of appropriate multiple cloning sites on the vector. Klehr et al. already demonstrated the use of BamHI and EcorRI sites to clone the MAR into a vector. The ordinary skill in the art would pick appropriate restriction sites to clone DNA sequence into a vector, wherein such knowledge and reagent is readily be available to an ordinary artisan at the time of filing, for example, the New England biolab catalog. Adding different linkers including BamHI and BglII would have been routine experimentation to an ordinary artisan at the time the invention was made. Therefore, the claimed invention would have been *prima facie* obvious in view of the cited reference.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CELINE X. QIAN whose telephone number is (571)272-0777. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Celine X Qian /
Primary Examiner, Art Unit 1636